Validation of Circumferential Carotid Artery Strain as a Screening Tool for Subclinical Atherosclerosis

Hyo Eun Park1, Goo-Yeong Cho2, Hyung-Kwan Kim3, Yong-Jin Kim3 and Dae-Won Sohn3

1 Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine, Cardiovascular Center, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Korea
2 Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine, Cardiovascular Center, Seoul National University Bundang Hospital, Seoul, Korea
3 Division of Cardiology, Department of Internal Medicine, Seoul National University College of Medicine, Cardiovascular Center, Seoul National University Hospital, Seoul, Korea

Aim: We evaluated the validity of circumferential carotid artery strain as a marker for subclinical atherosclerosis and its benefit in addition to carotid intima-media thickness (IMT) to detect high-risk groups.

Methods: The study was a cross-sectional study. From April 2007 to July 2008, 1057 patients who had undergone both echocardiography and carotid ultrasonography were consecutively enrolled. Circumferential carotid strain was obtained from the ratio of change in circular length during the cardiac cycle.

Results: As the number of risk factors for atherosclerosis increased from 0 to ≥4, circumferential strain decreased accordingly (5.1 ± 2.1, 4.4 ± 1.8, 3.8 ± 1.6, 3.3 ± 1.3, 3.1 ± 1.3%, p < 0.001), whereas carotid IMT and β-stiffness increased (p < 0.001 for both IMT and β-stiffness). Patients with a high Framingham risk score (FRS) also showed lower circumferential strain (5.01 ± 2.19, 3.46 ± 1.34, 3.08 ± 1.38, p < 0.001 for FRS < 5%, 5-15% and > 15%). Compared to patients with documented atherosclerotic disease, patients without known atherosclerotic disease showed significantly higher circumferential strain (3.25 ± 1.30 vs. 4.18 ± 1.89%, p < 0.001 for patients with vs. without documented atherosclerotic disease). The addition of circumferential carotid strain to IMT significantly improved the ability to detect patients at high risk for coronary heart disease, as assessed by the Framingham risk score (X2 = 61.0 from 42.4, p < 0.001), whereas β-stiffness did not have additive power (p = 0.439).

Conclusion: Circumferential strain can be used as a screening tool for subclinical atherosclerosis and may help detect subjects at increased risk for atherosclerotic disease.


Key words: Carotid artery, Atherosclerosis, Framingham risk score

Introduction

Atherosclerosis is a systemic disease, which is caused and affected by multiple risk factors. Mechanical stress is an important factor in atherosclerosis of the carotid artery1-5, and structural and functional parameters of the common carotid artery have been assessed in various studies. Carotid intima-media thickness (IMT) is a strong surrogate marker of coronary atherosclerosis, demonstrating a positive relationship with cardiovascular and cerebrovascular events6,7. Traditional risk factors such as male sex, aging, obesity, hypertension, diabetes mellitus and smoking have shown positive association with carotid IMT in multiple observational and epidemiological studies8-14. These risk factors were also significantly associated with changes in mechanical indices, and the accumulation of risk factors caused further deterioration of
mechanical indices independent of carotid atherosclerosis. High stretch stimulus and shear stress seem to play important roles in carotid atherosclerosis, which are reflected by mechanical indices; however, there are limitations in assessing mechanical stress. Since the arterial wall is not homogeneous, parameters such as β-stiffness assume that homogeneity of the wall may be unrealistic and inaccurate. In addition, luminal distensibility of the carotid artery using changes in luminal diameters cannot reflect whole arterial wall stress, and is often difficult to assess in cases of poorly defined intima to adventitia. Circumferential strain on the carotid artery using speckle tracking is a simple method, and yet has not been validated in a large population.

We sought to evaluate the validity of circumferential carotid artery strain as a marker for subclinical atherosclerosis and determine its additional benefit to carotid IMT in detecting high-risk groups based on the NCEP/ATP III (National Cholesterol Education Program’s Third Adult Treatment Panel) risk score.

Method

Study Population
The study was performed as a cross-sectional study. From April 2007 to July 2008, 1150 Korean patients who had undergone both echocardiography and carotid ultrasonography at Seoul National University Bundang Hospital were enrolled consecutively, regardless of the reason for the exam. Patients with atrial fibrillation or significant valvular heart disease were not included. After the exclusion of 11 patients less than 16 years old or over 85 years old, 66 patients with left ventricular dysfunction (ejection fraction <50%), and 18 patients with poor image quality, 1057 patients were included in the analysis (two patients were over 85 and had LV dysfunction). Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg without medication in the outpatient clinic with at least two separate measurements or use of antihypertensive medications. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dL, 2-hour blood glucose level after oral glucose tolerance test ≥200 mg/dL or use of diabetes medication. Dyslipidemia was defined as total cholesterol ≥240 mg/dL, and/or HDL cholesterol <40 mg/dL (men) or <50 mg/dL (women), triglyceride ≥150 mg/dL and/or use of lipid-lowering medications. Obesity was defined as body mass index (BMI) ≥25 kg/m². Documented atherosclerosis included patients with coronary artery disease, stroke or peripheral artery disease (history of intervention or >50% stenosis on imaging studies, or an ankle-brachial index of <0.9). The Framingham risk score (FRS) was derived from on-line NCEP/ATP-III guidelines. Risk factors of atherosclerosis were defined as age >55 in males and 65 in females, obesity, smoking history, dyslipidemia, hypertension and diabetes mellitus. The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital.

Transthoracic Echocardiography and Carotid Ultrasonography
Transthoracic two-dimensional echocardiography was performed using Vivid 7 (GE, Horton, Norway) at a single center. Routine echocardiographic examinations included measurements of left ventricular (LV) end-diastolic and end-systolic wall thicknesses, LV end-diastolic and end-systolic volumes, and LV ejection fraction (LV-EF) using the modified Simpson’s method, pulsed-wave Doppler examination of the mitral inflow, and pulsed-wave tissue Doppler imaging at the medial mitral annulus.

Carotid ultrasound of both right and left common carotid arteries was performed and stored digitally on a magneto-optical disk, then analyzed using Echopac (GE, Norway). The mean values for both carotid arteries were used for the analysis. After delineation of the walls of both carotid arteries, mean IMT was defined as the mean value of 200 points from the carotid bulb to 10 mm proximal to the bulb, and was measured at the R wave on the electrocardiogram (Fig. 1A). The carotid bulb was defined as a slight dilation in the carotid artery at its bifurcation into the external and internal carotid arteries. Other mechanical indices of the carotid artery such as luminal distensibility and β-stiffness were calculated using the following formulae:

\[ \text{Luminal distensibility (\%)} = \frac{[(D_s-D_d)/D_d]}{\text{distensibility}} \times 100 \]

\[ \beta\text{-Stiffness} = \frac{\ln (\text{SBP/DBP})}{\text{distensibility}} \]

where \( D_s(d) \) is the carotid artery dimension at systole (diastole), \( S(DBP) \) is systolic (diastolic) blood pressure.

Global circumferential strain was obtained from the short-axis view of the common carotid artery. The circumferential carotid arterial wall is regarded as a single circle (or one big segment). Circumferential strain is the percent change of the circumferential arterial wall during the cardiac cycle. Using off-line software, we manually traced the intima in the end-systolic phase. The arterial wall was automatically tracked and the peak positive value was obtained for analysis (Fig. 1B):
Global circumferential strain (\%) = \frac{[L(ES)-L(ED)]}{L(ED)} \times 100

where L(ES) or (ED) is the circular length at end-systole or end-diastole. The different colors shown in Fig. 1B represents six different segments included in the strain analysis, and the white dotted line represents the global circumferential strain value from the whole carotid wall. We considered it acceptable when five or more segments were tracked in strain analysis.

**Statistical Analysis**

Continuous variables are expressed as the mean ± standard deviation (SD), and categorical variables as frequencies and percentages. ANOVA was performed to compare continuous variables in different groups. Bivariate regression analysis was used to evaluate the correlation between continuous variables. To evaluate the additional prognostic power of each parameters such as strain, distensibility or β-stiffness in addition to carotid IMT in detecting high-risk groups with FRS ≥ 15%, we performed z-statistics using \( \chi^2 \) values from logistic regression analysis. We calculated the correlation coefficient to assess the intra- and inter-observer reproducibility of circumferential strain. All statistical analyses were performed with SPSS 17.0.

---

**Fig. 1.** A representative figure showing the measurement of carotid intima-media thickness (A) and circumferential carotid artery strain (B). From 1B, different colors represent six different segments included in strain analysis. White dotted line shown on the right side of supplementary figure 1B represents the global circumferential strain value from the whole carotid wall.
diabetes mellitus, and 482 patients (45.6%) had hypertension. Echocardiographic and carotid parameters are included in Table 1. The average LV-EF was 59.7%. Mean carotid IMT was 0.66 mm and \( \beta \)-stiffness was 0.08. The mean luminal distensibility was 7.70%, and circumferential strain of the common carotid artery was 3.99%. The feasibility of circumferential strain was 92.7%. The correlation coefficient was 0.93 for intra- and 0.90 for inter-observer measurement.

Subgroup Analysis According to NCEP/ATP-III Risk Score

The patients were grouped into low-risk (<5%),

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Mean ± SD or n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53 ± 16</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>522 (49.4%)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>126 ± 19</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>75 ± 12</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>157 (14.9%)</td>
</tr>
<tr>
<td>HTN, n (%)</td>
<td>482 (45.6%)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>303 (28.7%)</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>386 (36.5%)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>304 (28.8%)</td>
</tr>
<tr>
<td>Medication, n (%)</td>
<td></td>
</tr>
<tr>
<td>Antplatelet agent</td>
<td>316 (29.9%)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>251 (23.7%)</td>
</tr>
<tr>
<td>CCB</td>
<td>159 (15.0%)</td>
</tr>
<tr>
<td>ACE Inhibitor or ARB</td>
<td>312 (29.5%)</td>
</tr>
<tr>
<td>Statin</td>
<td>241 (22.8%)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>186 ± 42</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>132 ± 88</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>52 ± 15</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>108 ± 37</td>
</tr>
<tr>
<td>Echocardiographic parameters</td>
<td></td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>68.8 ± 15.8</td>
</tr>
<tr>
<td>LV-EF (%)</td>
<td>59.7 ± 6.7</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.14 ± 0.52</td>
</tr>
<tr>
<td>DT (msec)</td>
<td>210 ± 45</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>89.1 ± 24.8</td>
</tr>
<tr>
<td>Carotid parameters</td>
<td></td>
</tr>
<tr>
<td>IMT, mean (mm)</td>
<td>0.66 ± 0.16</td>
</tr>
<tr>
<td>Luminal distensibility (%)</td>
<td>7.70 ± 3.43</td>
</tr>
<tr>
<td>Circumferential strain (%)</td>
<td>3.99 ± 1.82</td>
</tr>
<tr>
<td>( \beta )-stiffness</td>
<td>0.08 ± 0.04</td>
</tr>
</tbody>
</table>

ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, CCB: calcium-channel blocker, DT: deceleration time of E wave, DM: diabetes mellitus, DBP: diastolic blood pressure, E: early mitral inflow velocity, HTN: hypertension, IMT: intima-media thickness, A: late diastolic mitral inflow velocity, LV-EF: Left ventricular ejection fraction by biplane modified Simpson’s method, LV/Ed(s); LV end-diastolic (end-systolic) dimension, LV-ED(S)V; LV end-diastolic (end-systolic) volume, LVMi; LV mass index, E(p); Peterson’s elastic modulus, SBP: systolic blood pressure

(SPSS Inc., Chicago, IL), and \( p < 0.05 \) was considered significant.

### Results

**Baseline Characteristics**

Baseline characteristics of the patients are shown in Table 1. Mean age of patients was 53 years, 522 patients (49.4%) were male, 157 patients (14.9%) had diabetes mellitus, and 482 patients (45.6%) had hypertension. Echocardiographic and carotid parameters are included in Table 1. The average LV-EF was 59.7%. Mean carotid IMT was 0.66 mm and \( \beta \)-stiffness was 0.08. The mean luminal distensibility was 7.70%, and circumferential strain of the common carotid artery was 3.99%. The feasibility of circumferential strain was 92.7%. The correlation coefficient was 0.93 for intra- and 0.90 for inter-observer measurement.

**Subgroup Analysis According to NCEP/ATP-III Risk Score**

The patients were grouped into low-risk (<5%),

![Fig. 2. Correlation analysis of circumferential carotid artery strain with age (A) and with carotid intima-media thickness (B).](image-url)
and diastolic function and carotid function worsened; IMT (0.53 ± 0.09, 0.62 ± 0.14, 0.67 ± 0.14, 0.74 ± 0.17, 0.77 ± 0.16; from 0 to ≥4 risk factors, p < 0.001), β-stiffness (0.06 ± 0.03, 0.07 ± 0.03, 0.08 ± 0.04, 0.10 ± 0.05, 0.10 ± 0.05; from 0 to ≥4 risk factors, p < 0.001), luminal distensibility (9.9 ± 3.8, 8.4 ± 3.4, 7.2 ± 3.1, 6.3 ± 2.7, 6.2 ± 2.4; from 0 to ≥4 risk factors, p < 0.001) and circumferential strain (5.1 ± 2.1, 4.4 ± 1.8, 3.8 ± 1.6, 3.3 ± 1.3, 3.1 ± 1.3; from 0 to ≥4 risk factors, p < 0.001, Fig. 4).

Subgroup Analysis According to the Presence of Documented Atherosclerotic Disease

Patients were then divided into two groups; group I with documented atherosclerosis (n=216) and group II without (n=841). Compared with group II, group I showed greater carotid IMT (0.78 ± 0.17 vs. 0.63 ± 0.15, p < 0.001) and β-stiffness (0.10 ± 0.05 vs. 0.08 ± 0.04, p < 0.001). Circumferential strain and luminal distensibility were both lower in group I (3.25 ± 1.30 vs. 4.18 ± 1.89, p < 0.001 for circumferential strain; 6.34 ± 2.56 vs. 8.03 ± 3.53, p < 0.001 for luminal distensibility in group I vs. II respectively).

Circumferential Carotid Strain as a Predictor of High-Risk Score

Using χ² values from logistic regression analysis, we evaluated the prognostic power of circumferential carotid strain, luminal distensibility and β-stiffness in addition to IMT to detect patients with high NCEP/ATP-III risk scores. Whereas luminal distensibility and β-stiffness did not increase prognostic power signifi-
reflecting stiffness. As a screening tool for subclinical atherosclerosis, we have shown the incremental diagnostic value of circumferential carotid strain in addition to carotid IMT in detecting high-risk patients. The Framingham risk score is used to help clinicians estimate a patient’s absolute risk for developing coronary heart disease (CHD). NCEP/ATP-III developed a modified, multivariable risk assessment tool to estimate absolute 10-year risk for CHD using seven traditional risk factors: sex, age, total cholesterol concentration, high-density lipoprotein cholesterol concentration, smoking status, systolic blood pressure, and current treatment for hypertension. Although NCEP/ATP-III guidelines are widely used in risk stratification for cardiovascular disease, there are weaknesses and limitations in their application in clinical practice. The study population consisted of mostly white middle-class individuals, and few validation studies of different ethnic or socioeconomic groups have been performed. As shown from substudies, recalibration including the different prevalence of risk factors and underlying rates of CHD is required when applying to other ethnicities. Furthermore, FRS may not be accurate in young individuals and women, due to the inability to stratify risk in subgroups that are CHD equivalent, such as diabetes or peripheral arterial disease, or in subgroups with multiple risk factors. The prevalence of risk factors and associated diseases vary in different ethnic groups, and the lack

![Fig. 5. Prognostic power of circumferential carotid artery strain to predict a high NCEP/ATP-III risk score (≥15%); incremental model by logistic regression analysis. P-values comparing additive predictive value of parameters are shown. Circumferential strain in addition to IMT shows a significant increase in predictive power when compared to IMT alone, whereas stiffness or luminal strain do not have additive benefits.](image)

cantly ($p=0.134$ for luminal distensibility; $p=0.100$ for $\beta$-stiffness), circumferential carotid strain significantly increased prognostic power ($\chi^2=61.0$ from 42.4, $p<0.001$). $\beta$-Stiffness did not add prognostic value to the combination of IMT and circumferential strain ($p=0.439$). The additional benefit of circumferential carotid strain in the detection of a high NCEP/ATP-III risk score is shown in Fig. 5.

**Discussion**

Carotid IMT is a strong surrogate marker of atherosclerosis, which is influenced by multiple systemic risk factors and mechanical indices of the carotid artery. Along with carotid IMT, mechanical indices were evaluated in various studies, especially their roles in atherosclerosis; however, there are limitations in using mechanical indices in clinical practice, because complicated calculations and systolic blood pressure at the time of measurement are required. The luminal distensibility of the carotid artery using changes in luminal diameters has limitations in that it cannot reflect whole arterial wall stress and is often difficult to assess in the case of poorly defined intima to adventitia; however, we have demonstrated that the determination of circumferential carotid artery strain is a simple and highly feasible method, and that decreased circumferential carotid strain correlates with increased carotid IMT and various mechanical indices reflecting stiffness. As a screening tool for subclinical atherosclerosis, we have shown the incremental diagnostic value of circumferential carotid strain in addition to carotid IMT in detecting high-risk patients.

The Framingham risk score is used to help clinicians estimate a patient’s absolute risk for developing coronary heart disease (CHD). NCEP/ATP-III developed a modified, multivariable risk assessment tool to estimate absolute 10-year risk for CHD using seven traditional risk factors: sex, age, total cholesterol concentration, high-density lipoprotein cholesterol concentration, smoking status, systolic blood pressure, and current treatment for hypertension. Although NCEP/ATP-III guidelines are widely used in risk stratification for cardiovascular disease, there are weaknesses and limitations in their application in clinical practice. The study population consisted of mostly white middle-class individuals, and few validation studies of different ethnic or socioeconomic groups have been performed. As shown from substudies, recalibration including the different prevalence of risk factors and underlying rates of CHD is required when applying to other ethnicities. Furthermore, FRS may not be accurate in young individuals and women, due to the inability to stratify risk in subgroups that are CHD equivalent, such as diabetes or peripheral arterial disease, or in subgroups with multiple risk factors. The prevalence of risk factors and associated diseases vary in different ethnic groups, and the lack
Circumferential Carotid Strain and Atherosclerosis

355

of standard criteria for Asian populations makes it difficult to apply FRS or NCEP/ATP-III guidelines directly to Asian patients in daily practice. Recently, efforts to update current guidelines have focused on preventive medicine. In a retrospective analysis of 284 young adults with acute myocardial infarction, 50% of the patients did not have multiple risk factors; demonstrating that current guidelines and risk factor analysis may not be accurate tools for predicting the future development of cardiovascular events. In the SHAPE (Screening for Heart Attack Prevention and Education) guideline, risk prediction and treatment are based on the assessment of atherosclerosis, even at a subclinical stage, rather than on currently recommended risk factors. We have shown not only the diagnostic value of circumferential carotid strain itself, but also its additive prognostic power on top of carotid IMT. Recent papers have pointed out limitations of carotid IMT as an indicator of atherosclerosis, and recent meta-analysis reported that IMT changes do not accurately predict the benefits of therapeutic interventions for cardiovascular risk factors. Thus, additional diagnostic modalities may help to discriminate patients with subclinical atherosclerosis and, by measuring circumferential carotid artery strain, we can obtain additive information on top of the known parameters of atherosclerosis.

Limitations

There are some limitations in acquiring circumferential carotid artery strain. The first and greatest limitation is that it requires off-line software for analysis, which sometimes limits its use at the bedside; however, it only takes a few minutes. Another limitation is that it is not 100% feasible to obtain circumferential carotid artery strain. For strain analysis, at least 5 segments should be traced, and thus, those with poor image quality may not be able to be examined; however, as we have shown, the feasibility of circumferential carotid artery strain was 92.7%, with good reproducibility data (correlation coefficient of 0.93 for intra-observer and 0.90 for inter-observer measurement). It is also more of a functional parameter, which distinguishes the significance of circumferential strain from IMT, an anatomical parameter.

Conclusion

The use of circumferential strain of the carotid artery as a marker for subclinical atherosclerosis is highly feasible, and this measurement is well correlated with conventional mechanical indices and carotid IMT. This marker improves the ability to detect patients at high risk for atherosclerosis, as defined by an NCEP/ATP-III risk score of ≥15%.

Funding Sources

The present study was supported by grants from the Korean Institute of Medicine 2008.

Disclosures

None

References

32) Goldberger ZD, Valle JA, Danekar VK, Chan PS, Ko DT, Nallamothu BK. Am Heart J, 2010; 160: 701-714